World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2025 September 9; 14(3): 105350

DOI: 10.5492/wjccm.v14.i3.105350

ISSN 2220-3141 (online)

MINIREVIEWS

Methylene blue in the critical care setting

Praveen Reddy Elmati, Teja Nagaradona, Vikas Raghove, Gowthami Sai Kogilathota Jagirdhar, Salim Surani

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade D
Scientific Significance: Grade C

P-Reviewer: Shelat VG

Received: January 20, 2025
Revised: March 21, 2025
Accepted: April 21, 2025
Published online: September 9, 2025
Processing time: 180 Days and 23.9 Hours

Praveen Reddy Elmati, Department of Anesthesiology, Saint Clair Hospital, Dover, NJ 07801, United States

Teja Nagaradona, Department of Medicine, St George University, School of Medicine, Granada SW17 0BD, West Indies

Vikas Raghove, Department of Anesthesia, IU Health Ball Memorial Hospital, Munice, IN 47303, United States

Gowthami Sai Kogilathota Jagirdhar, Department of Gastroenterology, Saint Michaels Medical Center, Newark, NJ 07107, United States

Salim Surani, Department of Medicine and Pharmacology, Texas AM University, College Station, TX 77843, United States

Corresponding author: Salim Surani, MD, Professor, Department of Medicine and Pharmacology, Texas AM University, 40 Bizzell Street, College Station, TX 77843, United States. srsurani@hotmail.com

Abstract

Methylene blue (MB) is a versatile medicine with a long history of use in various medical applications, including dye, antiseptic, and treatment for methemoglobinemia. It has a role in vasoconstriction, methemoglobin reduction, inhibition of guanylate cyclase, and anti-inflammatory effects. We reviewed PubMed and Google Scholar literature for relevant studies on MB in intensive care unit (ICU). We created search criteria using a combination of free text words, including MB, critical care, intensive care, sepsis, surgery, pharmacokinetics, and pharmacodynamics. Relevant articles published in the English language were analyzed and incorporated. MB has been used in managing patients with refractory shock, including septic shock, vasoplegic shock, surgical patients, and some instances of drug-induced hypotension. In conclusion, MB in the ICU is a promising medication for sepsis and vasoplegic shock. Further research with randomized trials on its long-term safety in the ICU, time of initiation, dose, and duration is necessary.

Key Words: Methylene blue; Critical care; Intensive care; Septic shock; Vasoplegic shock; Distributive shock

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

SHOUT
SHARE
IT

Core Tip: Methylene blue is a promising medication with various benefits due to its inhibition of guanylate cyclase, anti-inflammatory effects, and nitric oxide inhibition. It has been researched in septic shock, distributive shock in cardiac procedures, anaphylaxis, and organ transplant procedures. It is a safe medication based on literature with rare documented adverse events at lower doses. Its role as an adjunct to vasopressors needs to be further researched, including the definition of the dose, initiation time, and usage duration.

Citation: Elmati PR, Nagaradona T, Raghove V, Jagirdhar GSK, Surani S. Methylene blue in the critical care setting. *World J Crit Care Med* 2025; 14(3): 105350
URL: https://www.wjgnet.com/2220-3141/full/v14/i3/105350.htm
DOI: https://dx.doi.org/10.5492/wjccm.v14.i3.105350

INTRODUCTION

Methylene blue (MB) has a role in vasoconstriction, methemoglobin reduction, inhibition of guanylate cyclase[1], and anti-inflammatory effects. MB is a nitric oxide (NO) inhibitor[1]. It can reverse the vasodilation that occurs in septic shock patients[2]. It also prevents vasodilation in response to inflammatory cytokines, a sepsis hallmark. It is used in managing patients with refractory shock, including septic shock, distributive shock, surgical patients, and some instances of drug-induced hypotension. Hypotension, elevated lactate levels, and unresponsiveness to fluid administration characterize sepsis. It is a state of widespread vasodilation and decreased response to administered vasopressors. Given the reduced response to vasopressors and adverse events associated with vasopressors, research on alternative vasopressor-sparing drugs for sepsis is ongoing.

The vasoplegic syndrome is a state of sustained hypotension mean arterial pressure (MAP): 60 mmHg and low systemic vascular resistance (SVR) (< 800 dynes × second/cm^5) with organ hypoperfusion in patients with cardiac surgery, cardiopulmonary bypass surgery, liver transplantation syndrome, sepsis, anaphylaxis. Patients often have a normal or increased cardiac output (cardiac index ≥ 2.2 L/minute/m^2). Treatment is often with catecholamines and vasopressors[3]. MB increases vascular smooth muscle tone and is utilized in septic shock and vasoplegic shock. Ischemic reperfusion syndrome is another condition in which MB has been used for graft reperfusion[4]. Through its effects on the mitochondrial respiratory chain and NO production, MB has been used in metformin intoxication[5-10]. This article explores the current evidence on the mechanisms of action, indications, and clinical outcomes associated with MB in the intensive care unit (ICU) and perioperatively.

MECHANISM OF ACTION AND USE

MB is a versatile agent that has various effects on multiple pathways in the body. MB has been shown to restore vascular tone by inhibiting endothelial and inducible NO synthase and its downstream enzyme soluble guanylate cyclase[11]. Additionally, MB has been shown to restore vaso-regulation in vasoplegic conditions such as septic shock[11]. MB acts by inhibiting excessive NO production and alleviates its vasorelaxant effect in vascular smooth muscle, thus restoring vascular tone, allowing vasoconstriction to occur and increasing blood pressure[12].

Furthermore, MB has been evidenced to have neuroprotective effects, hypothesized to reduce brain injury and ischemia[13]. MB acts as a reducing agent for oxygen by adding electrons to the oxygen molecule. This reduction step allows methemoglobin to be converted to hemoglobin at an accelerated rate, thus decreasing the burden of patients afflicted with methemoglobinemia[14]. Figure 1 shows NO mediated vasodilation in shock and role of MB. MB has a short terminal half-life of 5.25 hours. Therefore, multiple repeated dosing of MB or continuous infusion may be required to maintain the drug's mechanism of action[15,16]. The lowest effective dose, ranging from 0.25-2 mg/kg/hour. has been documented[2,17]. Starting MB with vasopressors early in the onset of sepsis 8 hours is beneficial compared to late initiation[18]. MB is helpful as adjuvant therapy in shock rather than as rescue medication[12]. In vasoplegic syndrome, early administration while in the operating room was associated with better outcomes than postoperative ICU administration, with reduced major adverse events, including renal failure and operative mortality[19].

No adverse events were noted in the continuous infusion of MB over 48 hours[4,20]. Discoloration of skin and urine are the predominant non-fatal side effects in these patients[20]. Zhao *et al*[21] illustrates blue-green urine in his manuscript on methemoglobinemia due to nitrobenzene poisoning treated with MB. Adhit *et al*[22] illustrates similar urine on treatment of methemoglobinemia from pesticide positing with MB. High doses of MB > 7 mg/kg can compromise splanchnic perfusion[16]. MB is being studied as a potential therapy in hemorrhagic shock. Higher MAP on concomitant MB and blood transfusion administration was found in these animal studies[23-25].

INDICATIONS IN THE ICU

MB can be used in patients with distributive or vasodilatory shock including septic, vasoplegic shock or anaphylactic

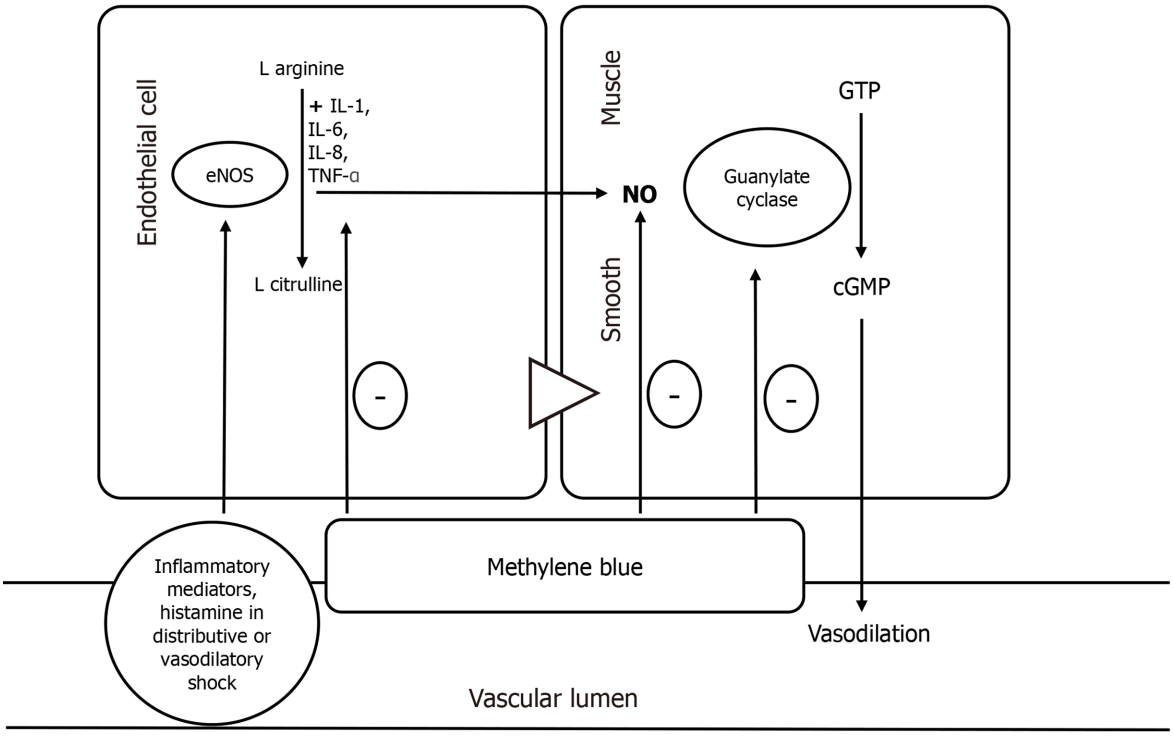

Figure 1 Mechanism of nitric oxide-mediated vasodilation in shock and the role of methylene blue. IL: Interleukin; TNF: Tumor necrosis factor; GTP: Guanosine triphosphate; cGMP: cyclic guanosine monophosphate; eNOS: Endothelial nitric oxide synthase.

shock that is associated with acute circulatory failure. It is associated with low MAP, altered cardiac output, and decreased SVR. Vasoplegic shock typically occurs after cardiac surgery (such as cardiopulmonary bypass) or due to other non-infectious causes. MB has been shown to decrease cyclic guanosine monophosphate levels and alleviate its vasorelaxant effect in patients with septic shock. MB can also scavenge NO, thus further reducing the vasorelaxant effects and improving pressure control[11].

In a systematic review by Ng *et al*[26] on randomized controlled trials (RCTs) with the use of MB in septic shock, the authors found 5 studies that used MB at a dose of 2 mg/kg increased MAP, reduced vasopressor usage, and increased ratio of arterial oxygen partial pressure to fraction of inspired oxygen. Reduction in mortality, serum lactate levels, and hospital length of stay was noted[26]. No differences in heart rate were noted in MB and the control group for heart rate changes. Alkazemi *et al*[27] reported 5 RCTs and 10 non RCTs on septic shock. The authors stated that there was a decreased in mortality in mortality on overall analysis and sub analysis of RTCs alone[27]. The presence of studies with small populations and heterogeneity is a limitation in multiple studies[12]. Table 1 shows the summary of individual studies on MB for shock and vasoplegic syndromes and Table 2 shows the summary of systematic reviews and meta-analyses on the use of MB in septic shock in patients.

For septic shock and vasoplegic syndrome, the dosage of MB is determined based on the clinical picture of the patient. Dosages started at an intravenous bolus of 2 mg/kg for 15 minutes, followed by escalating doses of 0.25-2 mg/kg/hour [28]. Other vasoplegic conditions, such as cardiac surgery, heart failure, and renal failure, cause an overall increase in levels of NO and activation of soluble guanylyl cyclase. NO will diffuse freely from the endothelium into the neighboring vascular smooth muscle, causing vasodilation, which may cause blood vessel relaxation by activating guanylyl cyclase. MB thus plays a role in modulating the effects of NO by decreasing levels of cyclic guanosine monophosphate and decreasing the effects of NO[29].

Huang *et al*[30] described the use of MB in patients with obstructive jaundice undergoing surgery. Procedures for indications include cholangiocarcinoma, duodenal adenocarcinoma, pancreatic carcinoma, hepatocellular carcinoma, chronic pancreatitis, biliary strictures, and stenosis. These patients are at risk of postoperative morbidity and mortality due to severe hypotension. 2 mg/kg of MB before anesthesia induction reduced the need to initiate noradrenaline and the dose of noradrenaline used. Biochemical indexes of liver and kidney function, including creatinine, glutamic oxalaacetic transaminase, glutamic-pyruvic transaminase, and creatine kinase, were lower post-procedure in patients in the MB group. Zhao *et al*[4] conducted a systematic review of 15 studies with 832 patients on MB for septic shock or vasoplegic syndrome and ischemia-reperfusion injury with similar results. The authors also saw an increase in MAP, heart rate, and peripheral vascular resistance. It has significant benefits in organ dysfunction, including lower incidence of renal failure and reduced lactate levels[4]. Luis-Silva *et al*[20] and Rajbanshi *et al*[31] state MB led to an immediate decrease in norepinephrine dosage and an earlier decrease in vasopressin dosage.

Hydroxocobalamin, a precursor of vitamin B12, inhibits NO and inflammatory mediators such as NO synthase, guanylate cyclase, and hydrogen sulfide. Administration of 5 g of hydroxocobalamin intravenous in 1-to-2 doses reduced vasopressor dose and improved MAP and SVR in refractory vasoplegic syndrome. Hiruy *et al*[32] compared hydroxocobalamin to MB in vasoplegic shock associated with cardiopulmonary bypass and found that hydroxocobalamin was

Table 1 Summary of individual studies on methylene blue for shock and vasoplegic syndromes

Author	Type of study	Indication	Dose for studies	Results
Zhu *et al*[24], 2008	Prospective study (animal study)	Septic shock	2 mg/kg IV	Higher MAP and lower plasma levels of TNF alpha, IL-6, IL-8, NO; and LA were observed in the MB group 12-hour survival rates were not statistically significant
Kirov *et al* [17], 2001	RCT	Septic shock	2 mg/kg IV bolus for 2 hours, followed by stepwise infusion of 0.25 mg/kg/hour, 0.5 mg/kg/hour, 1 mg/kg/hour, and 2 mg/kg/hour, that were maintained for 1 hour each	MB increased mean arterial pressure; vasopressor use decreased 87%, 81%, 40% respectively (P < 0.001) MB also reduced the body temperature and the plasma concentration of nitrates/nitrites and leukocytes
Luis-Silva *et al*[20], 2024	RCT	Septic shock	loading dose of MB (3 mg/kg) and maintenance (0.5 mg/kg/hour) for 48 hours	The MB group showed an immediate reduction in vasopressor use and higher IL-10 levels compared to the control group
Juffermans *et al*[16], 2010	RCT	Septic shock	1 mg/kg, 3 mg/kg, or 7 mg/kg over 20 minutes	Methylene blue had a dose-dependent effect on cardiac index, mean arterial, mean pulmonary artery and pulmonary artery occlusion pressures, left ventricular function, O(2) delivery and consumption and lactate levels Higher dose reduced splanchnic perfusion
Rajbanshi *et al*[31], 2023	Prospective study	Septic shock	Bolus dose with 2 mg/kg dose in 20 minutes	MAP in MB group increased (P = 0.005); vasopressor-free time increased (OR = 4.02, 95%CI: 1.18-13.68) No significant difference in terms of mortality, length of ICU stays, ventilator free days, and incidence of AKI
Hiruy *et al* [32], 2023	Retrospective cohort study	Vasoplegic shock post-cardiopulmonary bypass	Median bolus dose of methylene blue was 1.2 mg/kg. For patients administered a continuous infusion, the median dose was 0.25 mg/kg/hour for a median duration of 10 hours	Great reduction in vasopressor requirements and an increase in MAP were noted in the hydroxocobalamin group compared with the methylene blue group (P < 0.001)
Leyh *et al* [58], 2003	Prospective observational study	Norepinephrine-refractory vasoplegic shock after cardiopulmonary bypass	2 mg/kg IV over 20 minutes	SVR increased; norepinephrine use decreased (P < 0.05)
Mazzeffi *et al* [36], 2017	Retrospective cohort study	Post-cardiopulmonary bypass vasoplegic syndrome	MB doses were between 1 mg/kg and 2 mg/kg given as bolus over 10 minutes	MAP increased by 8 mmHg in MB group (P = 0.004)
Mehaffey *et al*[19], 2017	Retrospective study	Vasoplegic syndrome post - cardiopulmonary bypass	Bolus dose of 2 mg/kg IV MB followed by 12-hour infusion at 0.5 mg/kg/hour	Early MB uses improved survival and reduces the risk-adjusted rate of major adverse events in these patients (OR = 0.35, P = 0.037)
Shaker *et al* [2], 2025	RCT	Vasoplegic syndrome in cardiac surgery	MB bolus of 1 mg/kg or MB bolus of 4 mg/kg Followed by 0.25 mg/kg/hour infusion of MB for 72 hours after the bolus dose	Decreased time to vasopressor termination, and vasopressor-free days at 28 days The 4 mg/kg bolus dose group was protective against mortality with a hazard ratio of 0.29
Maslow *et al* [38], 2006	RCT	Hypotension during cardiopulmonary bypass and cardioplegic arrest	3 mg/kg IV	MAP increased, SVR increased, vasopressor use decreased (P < 0.05) Serum lactate levels were lower in MB patients
Ozal *et al* [37], 2005	Prospective study	Prevention of vasoplegic syndrome in coronary artery bypass graft surgery	2 mg/kg IV pre-op for more than 30 minutes	Reduces the incidence and severity of vasoplegic syndrome (0% *vs* 26%, P < 0.001); shortens both ICU and hospital stays
Huang *et al* [30], 2023	RCT	Hypotension in obstructive jaundice surgery	2 mg/kg IV	Noradrenaline use decreased (P = 0.017)
Luppi *et al* [23], 2024	RCTAnimal study	Animal study - hemorrhagic shock	Not specified	MAP recovery with MB + BT *vs* blood transfusion alone was significant (P < 0.05)
Ghiassi *et al* [25], 2004	RCTAnimal study	Refractory hemorrhagic shock	Not specified	Improved survival (P < 0.05), MAP increased, CO increased, and lactate decreased

MB: Methylene blue; IV: Intravenous; MAP: Mean arterial pressure; TNF: Tumor necrosis factor; IL-6: Interleukin-6; IL-8: Interleukin-8; NO: Nitric oxide; LA: Lactic acid; RCT: Randomized controlled trial; CI: Confidence interval; OR: Odds ratio; SVR: Systemic vascular resistance; ICU: Intensive care unit; AKI: Acute kidney injury; CO: Cardiac output; BT: Blood transfusion; Pre-op: Pre-operative..

Table 2 Summary of systematic reviews and meta-analyses on the use of methylene blue in shock and vasoplegic syndromes

Author	Type of study	Indication	Dose for studies	Results
Cadd *et al* [33], 2024	4 retrospective studies	263	Vasoplegic shock post-cardiopulmonary bypass	Hydroxocobalamin *vs* MB: Hydroxocobalamin was associated with a significant improvement in mean arterial pressure at 1 hour (MD: 5.30 mmHg, 95%CI: 2.98-7.62), total vasopressor dose at 1 hour (MD: -0.13 mcg/kg/minute NEE, 95%CI: -0.25 to -0.01) and total vasopressor dose at 6 hours (MD: -0.15 mcg/kg/minute NEE, 95%CI: -0.21 to -0.08) compared to MB
				No differences were observed in SVR or mortality between groups
Huang *et al* [39], 2024	6 RCTs	265	Septic shock, vasoplegic syndrome after cardiac surgery and ischemic reperfusion	MB reduced the duration of mechanical ventilation (MD: -0.68; 95%CI: -1.23 to -0.14), ICU LOS and (MD: -1.54, 95%CI: -2.61 to -0.48); hospital LOS (MD: -1.97; 95%CI: -3.92 to -0.11)
			Syndrome due to liver transplantation	No significant difference in mortality between the MB and placebo groups (ORs = 0.59; 95%CI: 0.32 to -1.06)
Zhao *et al*[4], 2022	10 RCT	832	Septic shock, vasoplegic syndrome and ischemic reperfusion	Mortality decreased (OR = 0.54, 95%CI: 0.34-0.85, P = 0.008); vasopressor use decreased (MD: -0.77, 95%CI: -1.26 to -0.28, P = 0.002)
	5 observational studies			MB increased MAP, HR and SVR. MB was associated with a lower incidence of renal failure. MB was linked to reduced lactate levels
Brokmeier *et al*[34], 2023	3 retrospective cohort studies	-	Vasoplegic shock post-cardiopulmonary bypass	Hydroxocobalamin *vs* MB: Hydroxocobalamin was associated with a higher MAP at 1 hour (MD: 7.80, 95%CI: 2.63-12.98); no difference in mortality (OR = 0.92, 95%CI: 0.42-2.03)
Ng *et al*[26], 2025	5 RCTs	257	Septic shock	MAP increased (MD: 8.4 mmHg, 95%CI: 5.01-11.75); mortality decreased (OR = 0.49, 95%CI: 0.27-0.88) reduced LOS (MD: -1.94 days, 95%CI: -3.79 to -0.08, P = 0.04, and increased PaO_2/FiO_2 (MD: 34.78, 95%CI: 8.94 to 60.61, P = 0.008)
Alkazemi *et al*[27], 2024	15 (5 RCTs, 10 observational studies)	441	Septic shock	Mortality decreased (OR = 0.52, 95%CI: 0.38-0.66, P < 0.001); ICU LOS decreased in 1 study; MAP increased post-infusion in 3 studies
Ballarin *et al* [12], 2024	3 RCTs	141	Septic shock	ICU LOS decreased (MD: -1.58, 95%CI: -2.97 to -0.20, P = 0.03); ventilation days decreased (MD: -0.72, 95%CI: -1.26 to -0.17, P = 0.01); time to vasopressor discontinuation decreased (MD: -31.49 hours, 95%CI: -46.02 to -16.96, P < 0.0001)

MB: Methylene blue; MAP: Mean arterial pressure; MD: Mean difference; CI: Confidence interval; NEE: Norepinephrine equivalent; SVR: Systemic vascular resistance; ICU: Intensive care unit; LOS: Length of stay; OR: Odds ratio; RCT: Randomized controlled trial; HR: Heart rate; PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fraction of inspired oxygen.

associated with a more significant reduction in vasopressor requirements than MB. Cadd *et al*[33] systematically compared hydroxocobalamin and MB in vasoplegic shock. The authors found 4 observational studies with 263 patients showing lower MAP and lower norepinephrine usage 1-6 hours after hydroxocobalamin administration. No benefits were noted with MB. In a similar meta-analysis by Brokmeier *et al*[34] on hydroxocobalamin the authors state the similarity between both drugs in relation to MAP and vasopressor dosage. Some authors, including Busse *et al*[35] suggested starting both hydroxocobalamin and MB when the norepinephrine dose exceeds > 0.05 μg/kg/minute in vasodilatory shock.

Mazzeffi *et al*[36] conducted a cohort study on eighty patients who received MB at a dose of 1 mg/kg and 2 mg/kg for post cardiopulmonary bypass vasoplegic syndrome. There was a decrease in MAP of 8 mmHg within 2 hours of administration[36]. Patients with deep hypothermic circulatory arrest and higher MAP at the time of MB had a better response [36]. Perioperative use of MB in patients at high risk of vasoplegic syndrome at a dose of 2 mg/kg reduced vasoplegic Syndrome occurrence by 26% compared to the placebo group. Patients had a history of angiotensin-converting enzyme inhibitors, calcium channel blockers, or heparin usage. They also had shorter ICU and more extended hospital stays[37]. Maslow *et al*[38] conducted a similar study and initiated MB at the onset of cardiopulmonary bypass in patients on angiotensin-converting enzyme inhibitors. The administration of MB increased MAP and SVR by 40 minutes and reduced the need for vasopressor administration. Furthermore, serum lactate levels were lower in MB patients, which signified better tissue perfusion.

Huang *et al*[39] describe a systematic review of six RCTs with 265 patients with distributive shock. The authors state no difference in mortality in both groups. There was a decrease in the duration of mechanical ventilation and length of stay in the hospital and ICU[39]. Doses ranging from 0.5 mg/kg to 3 mg/kg were given. There was a lack of a standard dose, a

high degree of heterogeneity, a lack of standardization among the vasopressors used, and variations in disease severity. The majority of the studies were of small sample size and may have a publication bias. Table 1 shows the summary of individual studies on MB for shock and vasoplegic syndromes and Table 2 shows the summary of systematic reviews and meta-analyses on the use of MB in vasoplegic shock in patients.

Case reports and case series exist on the use of MB for anaphylactic shock[40]. Evora *et al*[41] describes eleven patients in their systematic review of literature with anaphylactic shock that were treated with MB. Causes for anaphylaxis include protamine, iodinated dyes, penicillin and dipyrone. Administration of MB resulted in immediate recovery in all of the patients. Dosage of MB varied across case reports[41].

Methemoglobinemia

MB is the first-line treatment for methemoglobinemia. MB facilitates the reduction of methemoglobin to hemoglobin, restoring oxygen-carry capacity[42]. For methemoglobinemia, MB is started intravenously at a dosage of 1 mg/kg to 2 mg/kg. MB is generally a safe drug with dose-related hemolytic effect by interacting with methemoglobin and erythrocyte enzyme systems to reduce back to hemoglobin[43].

Drug-induced hypotension

A case report by Takahashi *et al*[44] states the utilization of MB for a patient with metformin toxicity and vasoplegic shock at a dose of one hundred milligrams of MB. There was a decrease in vasopressor requirement, an improvement in blood pressure, and a decrease in serum lactate level. The patient did not survive the admission. Katlan *et al*[45] report a similar case of metformin toxicity with 1 mg/kg, 30-60 minutes infusion of MB. The patient was discharged successfully on day 5. The authors suggest earlier administration for improved outcomes. Tackett *et al*[46] describe two patients in the surgical ICU with methemoglobinemia from benzocaine, a topical anesthetic, and dapsone used for pneumocystis pneumonia prophylaxis requiring MB administration.

SAFETY AND ADVERSE EFFECTS

MB has been considered a well-tolerated agent, with the main adverse effects being blue skin discoloration and, more commonly, urine. Other adverse effects that have been sighted were flushing, dizziness, nausea, and chest and limb pain [29]. MB has been shown to inhibit monoamine oxidase A in patients taking anti-depressants, which is responsible for serotonin breakdown in the brain. MB is an inhibitor of monoamine oxidase and can cause serotonin syndrome in patients taking serotonergic medications like tramadol, meperidine, fentanyl, linezolid, trazodone, serotonin-norepinephrine reuptake inhibitors, clomipramine, and selective serotonin reuptake inhibitors.

Therefore, in patients who require MB, careful consideration should be taken in patients taking anti-depressants to avoid this syndrome. Patients who are taking serotonergic agents have an increased risk of serotonergic syndrome with MB doses at 5 mg/kg[29,47]. MB also inhibits cytochrome P450; therefore, in patients who have hepatic or renal impairment, there is an increased toxicity burden[17]. MB is contraindicated in patients who have glucose-6-phosphate dehydrogenase (G6PD) deficiency due to increased risk of developing hemolytic anemia. G6PD is present in 5% of the population[48]. Vitamin C is one of the alternative medications used in G6PD deficiency patients[49-52]. It is also used when MB is unavailable, not tolerated well or as an add on agent when there is lack of improvement of methemoglobinemia with MB[53-56]. It is also used as an alternative to MB in patients with serotonergic syndrome as patients taking serotonergic medications are at high risk of serotonin toxicity with co-administration of MB [57].

Finally, MB is contraindicated in pregnant women as it is considered a pregnancy class X agent due to intestinal atresia and fetal death following an intra-amniotic injection[47]. Blue dye from MB can falsely lower the oxygen saturation on pulse oximeter readings due to the inhibition of light transmission from blue dye[35]. Alternatives for these patients include using a co-oximeter, arterial blood gas analysis or measuring methemoglobin levels in blood. Doses greater than 2 mg/kg can cause dose-dependent cardiac arrhythmia, coronary vasoconstriction, decreased gas exchange, lower cardiac output, and mesenteric and renal blood flow[58]. Mesenteric vasoconstriction and paradoxical methemoglobinemia are reported at 4 mg/kg[59].

CONCLUSION

MB is a valuable therapeutic agent in the ICU, particularly for managing refractory hypotension in septic shock, vasoplegic syndrome, and drug-induced hypotension. Further research is needed to establish its optimal dosing, administration, and impact on critical care outcomes.

FOOTNOTES

Author contributions: Elmati PR and Jagirdhar GSK designed the overall concept and outline of the manuscript; Elmati PR, Raghove V, Jagirdhar GSK, and Nagaradona T performed the research and analyzed the data; Elmati PR, Raghove V, Jagirdhar GSK, Nagaradona T, and Surani S contributed to the manuscript's writing and editing; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country of origin: United States

ORCID number: Praveen Reddy Elmati 0000-0003-1283-2368; Teja Nagaradona 0009-0005-0328-447X; Vikas Raghove 0000-0003-1544-5400; Gowthami Sai Kogilathota Jagirdhar 0000-0003-1855-0863; Salim Surani 0000-0001-7105-4266.

S-Editor: Bai Y
L-Editor: A
P-Editor: Zheng XM

REFERENCES

1 **Mayer B**, Brunner F, Schmidt K. Inhibition of nitric oxide synthesis by methylene blue. *Biochem Pharmacol* 1993; **45**: 367-374 [PMID: 7679577 DOI: 10.1016/0006-2952(93)90072-5] [FullText]
2 **Shaker EH**, Soliman AM, Bedewy AAE, Elrawas MM. Comparative study between high and low dose methylene blue infusion in septic cancer patients: a randomized, blinded, controlled study. *BMC Anesthesiol* 2025; **25**: 15 [PMID: 39780053 DOI: 10.1186/s12871-024-02792-3] [FullText]
3 **Ortoleva JP**, Cobey FC. A Systematic Approach to the Treatment of Vasoplegia Based on Recent Advances in Pharmacotherapy. *J Cardiothorac Vasc Anesth* 2019; **33**: 1310-1314 [PMID: 30598380 DOI: 10.1053/j.jvca.2018.11.025] [FullText]
4 **Zhao CC**, Zhai YJ, Hu ZJ, Huo Y, Li ZQ, Zhu GJ. Efficacy and safety of methylene blue in patients with vasodilatory shock: A systematic review and meta-analysis. *Front Med (Lausanne)* 2022; **9**: 950596 [PMID: 36237547 DOI: 10.3389/fmed.2022.950596] [FullText]
5 **Davis BJ**, Xie Z, Viollet B, Zou MH. Activation of the AMP-activated kinase by antidiabetes drug metformin stimulates nitric oxide synthesis in vivo by promoting the association of heat shock protein 90 and endothelial nitric oxide synthase. *Diabetes* 2006; **55**: 496-505 [PMID: 16443786 DOI: 10.2337/diabetes.55.02.06.db05-1064] [FullText]
6 **Duicu OM**, Privistirescu A, Wolf A, Petruş A, Dănilă MD, Raţiu CD, Muntean DM, Sturza A. Methylene blue improves mitochondrial respiration and decreases oxidative stress in a substrate-dependent manner in diabetic rat hearts. *Can J Physiol Pharmacol* 2017; **95**: 1376-1382 [PMID: 28738167 DOI: 10.1139/cjpp-2017-0074] [FullText]
7 **Gureev AP**, Samoylova NA, Potanina DV, Popov VN. The Effect of Methylene Blue and Its Metabolite-Azure I-on Bioenergetic Parameters of Intact Mouse Brain Mitochondria. *Biochem Mosc Suppl B Biomed Chem* 2022; **16**: 148-153 [PMID: 35601460 DOI: 10.1134/S1990750822020044] [FullText]
8 **Owen MR**, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. *Biochem J* 2000; **348** Pt 3: 607-614 [PMID: 10839993] [FullText]
9 **Sváb G**, Kokas M, Sipos I, Ambrus A, Tretter L. Methylene Blue Bridges the Inhibition and Produces Unusual Respiratory Changes in Complex III-Inhibited Mitochondria. Studies on Rats, Mice and Guinea Pigs. *Antioxidants (Basel)* 2021; **10**: 305 [PMID: 33669457 DOI: 10.3390/antiox10020305] [FullText]
10 **Tian WF**, Zeng S, Sheng Q, Chen JL, Weng P, Zhang XT, Yuan JJ, Pang QF, Wang ZQ. Methylene Blue Protects the Isolated Rat Lungs from Ischemia-Reperfusion Injury by Attenuating Mitochondrial Oxidative Damage. *Lung* 2018; **196**: 73-82 [PMID: 29204685 DOI: 10.1007/s00408-017-0072-8] [FullText]
11 **Fernando SM**, Tran A, Soliman K, Flynn B, Oommen T, Wenzhe L, Adhikari NKJ, Kanji S, Seely AJE, Fox-Robichaud AE, Wax RS, Cook DJ, Lamontagne F, Rochwerg B. Methylene Blue in Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Explor* 2024; **6**: e1110 [PMID: 38904978 DOI: 10.1097/CCE.0000000000001110] [FullText]
12 **Ballarin RS**, Lazzarin T, Zornoff L, Azevedo PS, Pereira FWL, Tanni SE, Minicucci MF. Methylene blue in sepsis and septic shock: a systematic review and meta-analysis. *Front Med (Lausanne)* 2024; **11**: 1366062 [PMID: 38698779 DOI: 10.3389/fmed.2024.1366062] [FullText]
13 **Isaev NK**, Genrikhs EE, Stelmashook EV. Methylene blue and its potential in the treatment of traumatic brain injury, brain ischemia, and Alzheimer's disease. *Rev Neurosci* 2024; **35**: 585-595 [PMID: 38530227 DOI: 10.1515/revneuro-2024-0007] [FullText]
14 **Capito JC**, Skaff BN, Kinney AR, Ashcraft AM. Methylene blue for hemolytic crisis in patients with met-hemoglobinemia secondary to hemoglobin volga: A case series. *J Family Med Prim Care* 2024; **13**: 2499-2502 [PMID: 39027866 DOI: 10.4103/jfmpc.jfmpc_1168_23] [FullText]
15 **Peter C**, Hongwan D, Küpfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharmacol* 2000; **56**: 247-250 [PMID: 10952480 DOI: 10.1007/s002280000124] [FullText]
16 **Juffermans NP**, Vervloet MG, Daemen-Gubbels CR, Binnekade JM, de Jong M, Groeneveld AB. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. *Nitric Oxide* 2010; **22**: 275-280 [PMID: 20109575 DOI: 10.1016/j.niox.2010.01.006] [FullText]
17 **Kirov MY**, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjørnsson B, Nedashkovsky EV, Bjertnaes LJ. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med* 2001; **29**: 1860-1867 [PMID: 11588440 DOI: 10.1097/00003246-200110000-00002] [FullText]
18 **Evora PR**, Ribeiro PJ, Vicente WV, Reis CL, Rodrigues AJ, Menardi AC, Alves Junior L, Evora PM, Bassetto S. Methylene blue for vasoplegic syndrome treatment in heart surgery: fifteen years of questions, answers, doubts and certainties. *Rev Bras Cir Cardiovasc* 2009; **24**: 279-288 [PMID: 20011872 DOI: 10.1590/s0102-76382009000400005] [FullText]

19 **Mehaffey JH**, Johnston LE, Hawkins RB, Charles EJ, Yarboro L, Kern JA, Ailawadi G, Kron IL, Ghanta RK. Methylene Blue for Vasoplegic Syndrome After Cardiac Operation: Early Administration Improves Survival. *Ann Thorac Surg* 2017; **104**: 36-41 [PMID: 28551045 DOI: 10.1016/j.athoracsur.2017.02.057] [FullText]

20 **Luis-Silva F**, Menegueti MG, Peres LM, Sepeda CDR, Jordani MC, Mestriner F, Petroski-Moraes BC, Brito-de-Sousa JP, Costa-Rocha IA, Cruz BL, Donadel MD, de Souza FB, Reis GHM, Bellissimo-Rodrigues F, Basile-Filho A, Becari C, Evora PRB, Martins-Filho OA, Auxiliadora-Martins M. Methylene blue therapy in addition to standard treatment for acute-phase septic shock: a pilot randomized controlled trial. *Front Med (Lausanne)* 2024; **11**: 1431321 [PMID: 39469142 DOI: 10.3389/fmed.2024.1431321] [FullText]

21 **Zhao L**, Jian T, Shi L, Li Y, Wen Z, Guo L, Li Q, Jian X. Case report: Methemoglobinemia caused by nitrobenzene poisoning. *Front Med (Lausanne)* 2023; **10**: 1096644 [PMID: 36895721 DOI: 10.3389/fmed.2023.1096644] [FullText]

22 **Adhit KK**, Menon S, Acharya S, K S. Toxin-Induced Methemoglobinemia With Kidney Injury and Hypoxic Brain Injury in a Case of Pesticide Poisoning: A Case Report. *Cureus* 2022; **14**: e32516 [PMID: 36654552 DOI: 10.7759/cureus.32516] [FullText]

23 **Luppi A**, Albuquerque AAS, Prandi M, Barbosa JM, Jordani MC, Ferraciolli SF, Wechsler S, Evora PRB. Methylene Blue and Blood Transfusion in Hemorrhagic Shock Resuscitation: An Experimental Porcine Study. *Braz J Cardiovasc Surg* 2024; **e20230480** [PMID: 39422346 DOI: 10.21470/1678-9741-2023-0480] [FullText]

24 **Zhu HD**, Yu CH, Wang HL, Wang Z, Yu XZ. [Effects of methylene blue on refractory hemorrhagic shock]. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2008; **30**: 136-139 [PMID: 18505111] [FullText]

25 **Ghiassi S**, Sun YS, Kim VB, Scott CM, Nifong LW, Rotondo MF, Chitwood WR Jr. Methylene blue enhancement of resuscitation after refractory hemorrhagic shock. *J Trauma* 2004; **57**: 515-521 [PMID: 15454796 DOI: 10.1097/01.ta.0000136159.22721.3d] [FullText]

26 **Ng KT**, Kwok PE, Lim WE, Teoh WY, Hasan MS, Zainal Abidin MF. The use of methylene blue in adult patients with septic shock: a systematic review and meta-analysis. *Braz J Anesthesiol* 2025; **75**: 844580 [PMID: 39615751 DOI: 10.1016/j.bjane.2024.844580] [FullText]

27 **Alkazemi A**, Almoosawy SA, Murad A, Alfares A. Methylene Blue for Septic Shock: A Systematic Review and Meta-analysis of Randomized and Prospective Observational Studies. *J Intensive Care Med* 2024; 8850666241300312 [PMID: 39574288 DOI: 10.1177/08850666241300312] [FullText]

28 **Busch CBE**, Bergman JJGHM, Nieuwdorp M, van Baar ACG. Role of the Intestine and Its Gut Microbiota in Metabolic Syndrome and Obesity. *Am J Gastroenterol* 2024; **119**: 1038-1046 [PMID: 38372280 DOI: 10.14309/ajg.0000000000002730] [FullText]

29 **Puntillo F**, Giglio M, Pasqualucci A, Brienza N, Paladini A, Varrassi G. Vasopressor-Sparing Action of Methylene Blue in Severe Sepsis and Shock: A Narrative Review. *Adv Ther* 2020; **37**: 3692-3706 [PMID: 32705530 DOI: 10.1007/s12325-020-01422-x] [FullText]

30 **Huang J**, Gao X, Wang M, Yang Z, Xiang L, Li Y, Yi B, Gu J, Wen J, Lu K, Zhao H, Ma D, Chen L, Ning J. Prophylactic Administration with Methylene Blue Improves Hemodynamic Stabilization During Obstructive Jaundice-Related Diseases' Operation: a Blinded Randomized Controlled Trial. *J Gastrointest Surg* 2023; **27**: 1837-1845 [PMID: 37101089 DOI: 10.1007/s11605-022-05499-3] [FullText]

31 **Rajbanshi LK**, Bajracharya A, Arjyal B, Devkota D. Can Use of Intravenous Methylene Blue Improve the Hemodynamics and Outcome of the Patients with Refractory Septic Shock? An Observational Study. *Indian J Crit Care Med* 2023; **27**: 669-674 [PMID: 37719353 DOI: 10.5005/jp-journals-10071-24535] [FullText]

32 **Hiruy A**, Ciapala S, Donaldson C, Wang L, Hohlfelder B. Hydroxocobalamin Versus Methylene Blue for the Treatment of Vasoplegic Shock Associated With Cardiopulmonary Bypass. *J Cardiothorac Vasc Anesth* 2023; **37**: 2228-2235 [PMID: 37586951 DOI: 10.1053/j.jvca.2023.07.015] [FullText]

33 **Cadd M**, Watson U, Kilpatrick T, Hardy B, Gallop L, Gerard A, Cabaret C. Hydroxocobalamin Versus Methylene Blue for Treatment of Vasoplegic Shock Following Cardiopulmonary Bypass: A Systematic Review and Meta-analysis. *J Cardiothorac Vasc Anesth* 2024; **38**: 3188-3199 [PMID: 39438181 DOI: 10.1053/j.jvca.2024.09.135] [FullText]

34 **Brokmeier HM**, Seelhammer TG, Nei SD, Gerberi DJ, Mara KC, Wittwer ED, Wieruszewski PM. Hydroxocobalamin for Vasodilatory Hypotension in Shock: A Systematic Review With Meta-Analysis for Comparison to Methylene Blue. *J Cardiothorac Vasc Anesth* 2023; **37**: 1757-1772 [PMID: 37147207 DOI: 10.1053/j.jvca.2023.04.006] [FullText]

35 **Busse LW**, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery-review of pathophysiology and update of treatment options. *Crit Care* 2020; **24**: 36 [PMID: 32019600 DOI: 10.1186/s13054-020-2743-8] [FullText]

36 **Mazzeffi M**, Hammer B, Chen E, Caridi-Scheible M, Ramsay J, Paciullo C. Methylene blue for postcardiopulmonary bypass vasoplegic syndrome: A cohort study. *Ann Card Anaesth* 2017; **20**: 178-181 [PMID: 28393777 DOI: 10.4103/aca.ACA_237_16] [FullText]

37 **Ozal E**, Kuralay E, Yildirim V, Kilic S, Bolcal C, Kücükarslan N, Günay C, Demirkilic U, Tatar H. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. *Ann Thorac Surg* 2005; **79**: 1615-1619 [PMID: 15854942 DOI: 10.1016/j.athoracsur.2004.10.038] [FullText]

38 **Maslow AD**, Stearns G, Butala P, Schwartz CS, Gough J, Singh AK. The hemodynamic effects of methylene blue when administered at the onset of cardiopulmonary bypass. *Anesth Analg* 2006; **103**: 2-8, table of contents [PMID: 16790616 DOI: 10.1213/01.ane.0000221261.25310.fe] [FullText]

39 **Huang X**, Yan W, Chen Z, Qian Y. Effect of methylene blue on outcomes in patients with distributive shock: a meta-analysis of randomised controlled trials. *BMJ Open* 2024; **14**: e080065 [PMID: 38216185 DOI: 10.1136/bmjopen-2023-080065] [FullText]

40 **Evora PR**, Roselino CH, Schiaveto PM. Methylene blue in anaphylactic shock. *Ann Emerg Med* 1997; **30**: 240 [PMID: 9250657 DOI: 10.1016/s0196-0644(97)70152-5] [FullText]

41 **Evora PR**, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. *Ann Allergy Asthma Immunol* 2007; **99**: 306-313 [PMID: 17941276 DOI: 10.1016/S1081-1206(10)60545-5] [FullText]

42 **Pushparajah Mak RS**, Liebelt EL. Methylene Blue: An Antidote for Methemoglobinemia and Beyond. *Pediatr Emerg Care* 2021; **37**: 474-477 [PMID: 34463662 DOI: 10.1097/PEC.0000000000002526] [FullText]

43 **Clifton J 2nd**, Leikin JB. Methylene blue. *Am J Ther* 2003; **10**: 289-291 [PMID: 12845393 DOI: 10.1097/00045391-200307000-00009] [FullText]

44 **Takahashi Y**, Nakano H, Motoki M, Wakimoto Y, Ikechi D, Koyama Y, Hashimoto H. Successful use of methylene blue for catecholamine-refractory vasoplegic shock due to metformin intoxication: A case report and literature review. *Acute Med Surg* 2024; **11**: e981 [PMID: 39010890 DOI: 10.1002/ams2.981] [FullText]

45 **Katlan B**. Methylene Blue in Metformin Intoxication: Not Just Rescue But Also Initial Treatment. *Pediatr Emerg Care* 2024; **40**: 818-821 [PMID: 38471766 DOI: 10.1097/PEC.0000000000003152] [FullText]

46 **Tackett N**, Mathews T, Mentzer C, Morrow C, Thurston B, Lombardozzi K. Acquired Methemoglobinemia in the Surgical Intensive Care

Unit. *Am Surg* 2023; **89**: 3959-3961 [PMID: 37303171 DOI: 10.1177/00031348231173959] [FullText]

47 **Bistas E**, Sanghavi DK. Methylene Blue. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan- [PMID: 32491525] [FullText]

48 **Visclosky T**, Schaeffer W, Pomeranz E, Ponce DM. Primaquine overdose in a toddler. *Am J Emerg Med* 2021; **45**: 676.e3-676.e5 [PMID: 33279327 DOI: 10.1016/j.ajem.2020.10.084] [FullText]

49 **Quinn J**, Gerber B, Fouche R, Kenyon K, Blom Z, Muthukanagaraj P. Effect of High-Dose Vitamin C Infusion in a Glucose-6-Phosphate Dehydrogenase-Deficient Patient. *Case Rep Med* 2017; **2017**: 5202606 [PMID: 29317868 DOI: 10.1155/2017/5202606] [FullText]

50 **Arun VJ**, Deorukhkar A, Rafi AM, Charles D, Devendra R, Innah SJ, Kedar P. Successful management of Methemoglobinemia and G6PD deficiency in a patient posted for surgical excision of branchial cyst. *Asian J Transfus Sci* 2022; **16**: 128-131 [PMID: 36199403 DOI: 10.4103/ajts.ajts_152_20] [FullText]

51 **Reeves DJ**, Saum LM, Birhiray R. I.V. ascorbic acid for treatment of apparent rasburicase-induced methemoglobinemia in a patient with acute kidney injury and assumed glucose-6-phosphate dehydrogenase deficiency. *Am J Health Syst Pharm* 2016; **73**: e238-e242 [PMID: 27099330 DOI: 10.2146/ajhp150591] [FullText]

52 **Vidhyashree BH**, Zuber M, Taj S, Venkataraman R, Sathish Kumar BP, Jabeen N. Rasburicase induced methemoglobinemia: A systematic review of descriptive studies. *J Oncol Pharm Pract* 2022; **28**: 1189-1206 [PMID: 35119341 DOI: 10.1177/10781552221075239] [FullText]

53 **Cantrell C**, Costers V, Wilson CC, Dudek CJ, Arnold JK. Refractory Methemoglobinemia Secondary to Topical Dapsone With Subsequent Autoimmune Hemolytic Anemia. *Cureus* 2022; **14**: e28811 [PMID: 36225525 DOI: 10.7759/cureus.28811] [FullText]

54 **Rino PB**, Scolnik D, Fustiñana A, Mitelpunkt A, Glatstein M. Ascorbic acid for the treatment of methemoglobinemia: the experience of a large tertiary care pediatric hospital. *Am J Ther* 2014; **21**: 240-243 [PMID: 24914501 DOI: 10.1097/MJT.0000000000000028] [FullText]

55 **Keats KR**, Robinson R, Patel M, Wallace A, Albrecht S. Ascorbic Acid for Methemoglobinemia Treatment: A Case Report and Literature Review. *J Pharm Pract* 2024; **37**: 1015-1020 [PMID: 37421600 DOI: 10.1177/08971900231188834] [FullText]

56 **Hammami MB**, Qasim A, Thakur R, Vegivinti CTR, Patton CD, Vikash S, Kumar A. Rasburicase-induced hemolytic anemia and methemoglobinemia: a systematic review of current reports. *Ann Hematol* 2024; **103**: 3399-3411 [PMID: 37468669 DOI: 10.1007/s00277-023-05364-6] [FullText]

57 **Hamza A**, Nasrullah A, Singh R, DiSilvio B. Phenazopyridine-Induced Methaemoglobinaemia The Aftermath of Dysuria Treatment. *Eur J Case Rep Intern Med* 2022; **9**: 003191 [PMID: 35265556 DOI: 10.12890/2022_003191] [FullText]

58 **Leyh RG**, Kofidis T, Strüber M, Fischer S, Knobloch K, Wachsmann B, Hagl C, Simon AR, Haverich A. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? *J Thorac Cardiovasc Surg* 2003; **125**: 1426-1431 [PMID: 12830064 DOI: 10.1016/s0022-5223(02)73284-4] [FullText]

59 **Arias-Ortiz J**, Vincent JL. Administration of methylene blue in septic shock: pros and cons. *Crit Care* 2024; **28**: 46 [PMID: 38365828 DOI: 10.1186/s13054-024-04839-w] [FullText]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2025 Baishideng Publishing Group Inc. All rights reserved.